General

Guideline Title

Management of chronic myeloid leukemia.

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Management of chronic myeloid leukemia. Edmonton (Alberta): CancerControl Alberta; 2012 Nov. 37 p. (Clinical practice guideline; no. LYHE-001). [98 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Staging and Prognosis

1. Staging of chronic myeloid leukemia (CML) according to the definitions set out by the World Health Organization (WHO) (Swerdlow et al., 2008):
    - The chronic phase (CP) is defined by peripheral blood blasts fewer than 10% in the blood and bone marrow.
    - The accelerated phase (AP) is defined as blasts 10% to 19% of white blood cells in peripheral and/or nucleated bone marrow cells, persistent thrombocytopenia ($<100 \times 10^9$/L) unrelated to therapy or persistent thrombocytosis ($>1000 \times 10^9$/L) unresponsive to therapy, increasing white blood cells and spleen size unresponsive to therapy, and cytogenetic evidence of clonal evolution.
    - The terminal blast crisis (BC) phase is defined by peripheral blood blasts ≥20% of peripheral blood white blood cells or nucleated bone marrow cells, extramedullary blast proliferation, and large foci or clusters of blasts on bone marrow biopsy.
2. The Sokal index and/or Hasford score are recommended for prognostication of newly-diagnosed patients with CML (LeukemiaNet, 2010). The European Treatment and Outcome Study (EUTOS) score (LeukemiaNet, 2011) can be used for patients being treated with a tyrosine kinase inhibitor (TKI) to predict complete cytogenetic response (CCyR) at 18 months.

Diagnosis and Baseline Investigations

3. The following investigations are recommended at diagnosis for all patients with suspected or confirmed CML:
    - Bone marrow aspirate and biopsy
    - Baseline bone marrow cytogenetics
    - Peripheral blood or bone marrow quantitative real-time polymerase chain reaction (Q-RT-PCR)

Treatment Options

4. Treatment with a TKI as first-line treatment for all newly-diagnosed CP-CML patients is recommended as the early response to a TKI can either reinforce or weaken the indication for allogeneic stem cell transplant (SCT). Currently in Alberta therapy is begun with one of the second generation TKIs, dasatinib or nilotinib. The choice of a second-generation TKI may be guided by an individual patient's comorbidities. Patients having achieved their therapeutic milestones with and tolerant of imatinib should continue on it.
5. A second-generation TKI (nilotinib or dasatinib) is recommended for patients with imatinib resistance/intolerance, or who fail to achieve any of the treatment milestones. The choice of a second-generation TKI may be guided by an individual patient's comorbidities. The presence of specific mutations will override other considerations when determining the optimal agent to employ. Patients eligible for transplant should be evaluated for possible transplantation given the lack of long-term efficacy data for second-generation agents.
6. Allogeneic SCT remains a treatment option as it is the only known cure; this option may be selected at any point during the treatment course based on informed patient preference. Allogeneic SCT is the preferred option in patients with evidence of clonal progression or with advanced-phase disease. The most effective treatment available should be employed while awaiting transplantation.
7. All transplant-eligible patients who fail second-line TKI therapy should be evaluated for transplantation before treatment with a third-line TKI is considered. Transplantation should be considered in patients with evidence of clonal progression by bone marrow cytogenetics.
8. Patients presenting with accelerated phase disease should be started on a TKI with early consideration given to transplantation.
9. Patients presenting with blast phase disease should be treated with induction type chemotherapy along with a TKI and early consideration should be given to transplantation.
10. Interferon-α (IFNα) should be considered only in patients who are unable to tolerate a TKI and are ineligible for SCT or entry in a clinical trial, or in women who wish to become pregnant. Treatment should be employed with the guidance of a physician with clinical experience using IFNα.

Monitoring Treatment Response

11. Peripheral blood Q-RT-PCR should be performed every 3 months. If a molecular response greater than 3-log reduction (major molecular response; MMR) is reached and stable for 2 years, the frequency of Q-RT-PCR may be decreased to every 4 to 6 months. Bone marrow karyotyping may be employed as an alternative to Q-RT-PCR until CCyR (<1% International Scale [IS]) is achieved. Bone marrow karyotyping may be performed at 1 year to confirm CCyR and to detect clonal progression or other abnormalities. Thereafter, marrow karyotyping should not be performed annually unless there are clonal abnormalities that need to be followed.
12. The recommended definitions of optimal treatment response are:
    - Complete hematologic response (CHR) and at least a 1-log reduction (±0.5) at 3 months (10% IS)
    - CCyR at 12 months (2-log reduction: 1% IS)
    - MMR at 18 months (≥3-log reduction: ≤0.1% IS)
13. The recommended definitions of primary treatment failure are:
    - <1-log reduction (± 0.5) (>10% IS) at 3 months
    - < CCyR at 12 months (2-log reduction: 1% IS)
    - < MMR at 18 months (3-log reduction: 0.1% IS)
14. Mutation testing is recommended in patients who fail to achieve treatment milestones, or if there is a loss of response. Mutational analysis should always be performed before switching TKIs.
15. Human leukocyte antigen (HLA) typing of the patient and siblings is recommended when a patient presents in AP or BC or when there is suboptimal response, loss of a previously obtained response or significant intolerance.
16. Monitoring for patients receiving a second-generation TKI should include:
    - Assessment of hematologic response conducted until CHR is achieved due to a high rate of cytopenias after initiation of TKI therapy
    - Q-RT-PCR of peripheral blood every three months until a 3-log reduction is achieved. The frequency of Q-RT-PCR monitoring may be decreased to every 4 to 6 months once MMR is reached and stable for 2 years. Bone marrow testing is recommended at 1 year after initiation of a second-generation agent to identify clonal progression.
17. Repeat cytogenetics and mutation testing after treatment with a second-generation TKI are advised if no improvement in therapeutic milestones or a loss of response is observed.
18. Second-line treatment failure with a second-generation TKI, in accordance with European Leukemia Net guidelines, are defined as:
    - No cytogenetic response (Philadelphia chromosome-positive [Ph+] >95%) or molecular response at 3 months.
    - Minimal cytogenetic response (Ph+ 66%–95%) or no molecular response at 6 months.
    - Less than a partial cytogenetic response (Ph+ >35%) or <0.5-log reduction (>0.35% IS) at 12 months.
19. Discontinuation of TKI therapy in responding patients is not recommended outside of a clinical trial.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic myeloid leukemia (CML)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Medical Genetics

Oncology

Pathology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To identify what diagnostic and baseline investigations, treatment options, and criteria for monitoring treatment response are recommended for adult patients with suspected or confirmed chronic myeloid leukemia (CML)

Target Population

Adults over 18 years of age with suspected or confirmed chronic myeloid leukemia (CML)

Note: Different principles apply to pediatric patients.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Staging of chronic myeloid leukemia (CML) according to the definitions set out by the World Health Organization (WHO)
2. Use of the Sokal index and/or Hasford score and the European Treatment and Outcome Study (EUTOS) score for prognostication
3. Bone marrow aspirate and biopsy
4. Baseline bone marrow cytogenetics
5. Peripheral blood or bone marrow quantitative real-time polymerase chain reaction (Q-RT-PCR)

Treatment/Management

1. Treatment with a tyrosine kinase inhibitor (TKI) (imatinib, dasatinib, nilotinib)
2. Allogeneic stem cell transplantation (SCT)
3. Interferon-α (IFNα)
4. Monitoring treatment response using peripheral blood Q-RT-PCR, mutation testing, human leukocyte antigen (HLA) typing

Major Outcomes Considered

- Sensitivity and predictive value of diagnostic and mutation tests
- Progression rate
- Survival rate (overall, 5-year, progression-free, event-free)
- Cytogenetic response rate
- Hematologic response rate
- Molecular response rate
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Questions

- What diagnostic and baseline investigations are recommended for adult patients with suspected or confirmed chronic myeloid leukemia (CML)?
- What are the recommended treatment options for CML?
- What are the criteria for monitoring response to treatment?

Search Strategy

This guideline adopts the 2012 recommendations developed by the Canadian Consensus Group on the Management of Chronic Myelogenous Leukemia, based closely on the European Leukemia Net Guidelines. In addition, guidelines developed by Cancer Care Ontario (CCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network, National Institute for Health and Care Excellence (NICE) were reviewed in the process of developing this document. Appendices A, B and C in the original guideline document summarize the most current recommendations from these agencies.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the Knowledge Management (KM) Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, the Guideline Utilization Resource Unit (GURU) does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Appendices A, B and C in the original guideline document summarize the most current recommendations from the reviewed guidelines.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

This guideline adopts the 2012 recommendations developed by the Canadian Consensus Group on the Management of Chronic Myelogenous Leukemia, based closely on the European Leukemia Net Guidelines. In addition, guidelines developed by Cancer Care Ontario (CCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network, National Institute for Health and Care Excellence (NICE) were reviewed in the process of developing this document.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline document was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

LeukemiaNet. Calculation of relative risk of CML patients. [internet]. 2010 [accessed 2012 Jul 18].

LeukemiaNet. Online calculation of the EUTOS score. [internet]. 2011 [accessed 2012 Jul 18].

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Fourth ed. Lyon (France): IARC; 2008.

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Portions of this guideline document were adapted, with permission, from recommendations developed and updated by the Canadian Consensus Group on the Management of Chronic Myelogenous Leukemia.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate management of chronic myeloid leukemia (CML)

Potential Harms

- All tyrosine kinase inhibitors (TKIs) should be used with caution in any patient with a history of cardiovascular disease, notably cardiac arrhythmias.
- Table 1 in the original guideline document presents comorbidities predicting adverse events during treatment with a second-generation TKI.
- Adverse events requiring treatment discontinuation occur more commonly with higher-dose imatinib.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

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Date Released

2012 Nov

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Hematology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Hematology Tumour Team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, pharmacists, and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 25, 2014.

Copyright Statement

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